

Managing Cholera as a Preventable Global Threat

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Abstract

The significant annual burden of disease from cholera remains a preventable global tragedy. An oral cholera vaccine (OCV) emergency stockpile represents a good beginning for improved global cholera management, and modeling studies suggest that realizing the greatest impacts of using OCVs for outbreak response depends on national preparedness. Using the stockpile will create opportunities to gain valuable evidence and experience about the potential role and relative cost-effectiveness of OCVs. It is time to see cholera as a serious and preventable global threat worthy of coordinated attention and management, active global surveillance, and increased human and financial resource investments. Stakeholders at all levels should seek to assess cholera risks and risk management opportunities and begin to collect improved evidence about the benefits, risks, and costs of new OCVs.

Keywords: Cholera; Global tragedy; Oral cholera vaccines

Introduction

The human experience with *Vibrio cholerae* continues to evolve [1] along with our understanding of the dynamics of transmission [2]. Symptomatic infections cause severe, acute watery diarrhea and vomiting, which can rapidly lead to dehydration and death if not aggressively treated. Cholera outbreaks can spread explosively through populations at risk [1] and quickly overwhelm health systems, which may lead to the use of scarce resources for crisis management instead of prevention [3]. Despite long-standing knowledge about how to control and locally eliminate cholera transmission [4], and despite evidence of effective maintenance of water and food safety, sanitation, and healthcare delivery systems that largely protect populations in developed countries from cholera [1,5], morbidity and mortality from this disease remain a global tragedy.

Seeing the global burden

Globally, over 200,000 reported cholera cases occur each year with increased incidence reported over the past 5 years [6]. Figure 1 shows the number of years for the period including 2000 through 2012 that individual countries reported cases of cholera. Hashed gray lines indicate countries that reported any imported cases during that time period, and small and large blue dots show the countries that reported more than 5,000 and 50,000 cases, respectively, in at least one year. In contrast to an annual or regional snapshot, mapping the cumulative global data reveals a clear global problem. Yet Figure 1 only tells part of the story, because surveillance quality remains an issue. Many countries inconsistently report cases, only report laboratory confirmed cases, and/or report cases to the WHO as "acute watery diarrhea, not otherwise specified" (not counted in Figure 1). Consequently, the true global annual burden of cholera may exceed 2.8 million cases (range 1.4 to 4.3 million) [7]. Cholera cases can impact any country, even if in developed countries cholera primarily occurs from isolated imported cases or limited local consumption of contaminated seafood that require investigation, treatment, and/or follow up. We suggest the need to manage cholera as a preventable global threat worthy of coordinated attention that requires active global surveillance and to address the potential role of oral cholera vaccines (OCVs) nationally, regionally, and globally in fighting cholera.

Role of OCVs

In 2012, a technical working group at the World Health Organization (WHO) took an important step in the direction of coordinated global cholera management by recommending the creation of a global OCV stockpile for use in emergencies [8,9]. Once available in late 2013, the OCV stockpile will represent a valuable resource for reactive vaccination to respond to cholera outbreaks, and it will provide an opportunity to gather necessary evidence to evaluate the role of OCVs. Demand for an OCV emergency stockpile steadily increased over the past decade, consistent with a shift away from a 1999 consensus that discouraged consideration of reactive OCV use based on characteristics of available OCVs then and other considerations [10]. More recent perspectives encourage countries to consider newer vaccines [11] as one of their many options in combating cholera [12-15]. The devastating cholera outbreak in Haiti in 2010-2011, for which health authorities relied on treatment and non-vaccine interventions, in part due to the lack of access to sufficient quantities of the vaccine [16,17], effectively tipped the scale toward creating an OCV stockpile. Considering the "perfect" as functional health systems, basic infrastructure for water and sanitation, and sufficient quantities of an ideal (i.e., highly-effective, inexpensive, easy-to-deliver) vaccine, consensus now exists that waiting for the "perfect" should not be the enemy of the "good" that may come from potentially using currently available OCVs to help reduce disease burdens during outbreaks.

Although we cannot know the impact that OCVs would have had in Haiti, several modeling studies suggested their use may have reduced cases and deaths [18-23]. Overall, the models suggest that when and how we use OCVs in an outbreak situation matters. OCVs promise the

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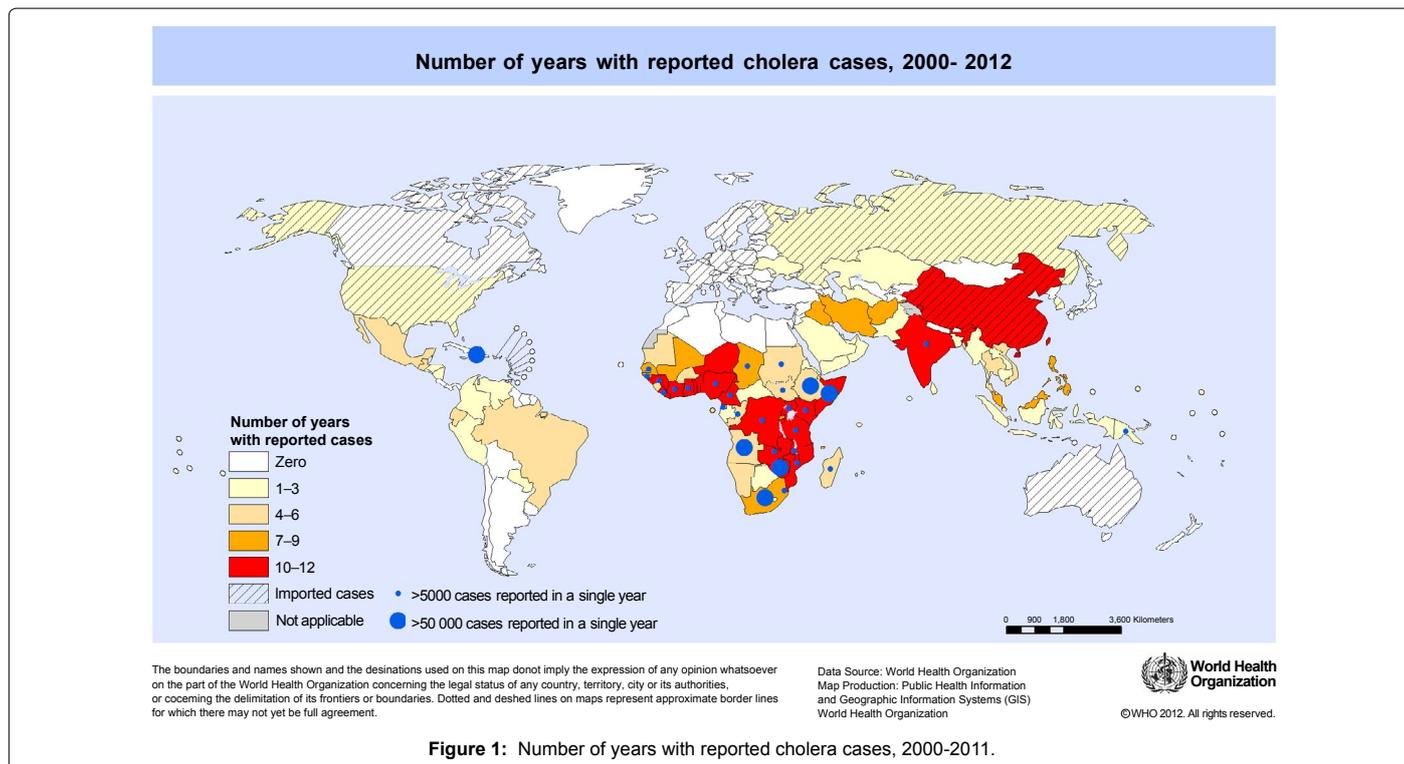


Figure 1: Number of years with reported cholera cases, 2000-2011.

largest benefits if used early with high coverage in high-risk areas. Too little or too late implies little benefit, particularly because the protection provided by currently available OCVs requires some time to develop (for instance, two doses given one to two weeks apart) and immunity wanes relatively quickly [19] (i.e., within several years [24]). Notably, the models found that once “cases appear in a region and local transmission is occurring, it may be too late to vaccinate for that season” [20] and “a limited vaccine supply provided late in the epidemic was projected to have a modest effect” [21]. While it might seem reasonable to vaccinate late to catch some of the population missed by the disease, the benefits attributable to the vaccine approach zero if individuals derive their immunity from becoming infected with cholera first (see discussion of this concept related to measles [25]). Thus, late reactive vaccination shifts the cost-effectiveness ratio considerably, which reinforces the concept that when it comes to outbreak response, faster is better [25,26]. Given limited and mixed experience with actual deployment of OCVs during outbreak response and in complex situations [13,14,27-34], the actual benefits of OCV uses from the stockpile remain uncertain and they require evaluation and documentation. In the short term, countries need to prepare to use OCVs and develop the capacity to evaluate the impact of reactive vaccination to control cholera epidemics.

Modeling insights

In light of existing uncertainties, modeling studies may offer important insights about what it will take to get value for money from the new OCV stockpile. At least five major uncertainties impact the effectiveness of OCV deployed from the stockpile. First, while growing evidence suggests that OCV use can provide some indirect protection to unvaccinated individuals [27,36,37], uncertainty remains about the ability of OCVs to disrupt transmission once an outbreak starts. Second, the potential population impacts of OCV use will depend on the extent to existing population immunity, with cholera control in immunologically naïve populations requiring higher and more rapid

OCV coverage to achieve control than in endemic areas [36]. Third, since OCV use in high-risk, immunologically naïve populations before an outbreak naturally offers the largest benefit, maximizing the economic benefits given the reality of limited available resources requires predicting where outbreak will occur and identifying high risk individuals *a priori* [20]. Fourth, although the models assume effective delivery of vaccine in a functional health system with access to all areas, these conditions may not exist following a natural disaster, in areas of conflict, or other complex emergency situations [21,38]. Fifth, cost-effectiveness of OCVs will represent an important consideration, because policy makers face real resource constraints and other options exist for cholera prevention, treatment, and control [39-42]. Recognition of all of the above factors points to the need for strategic preparedness. Thus, the best use of OCV from the stockpile will depend on national efforts to enhance surveillance, assess current population immunity and risks, identify high risk areas, create logistical plans, and prepare to rapidly and cost-effectively roll out plans to use OCV from the stockpile if needed and appropriate. While creating, using, and evaluating an OCV emergency stockpile represents a good beginning for improved global cholera management, much work remains to ensure optimal use. In addition, we must also ensure that “good” reactive uses of OCV from the emergency stockpile do not become the “enemy” of prevention and additional improvements toward the “perfect.”

Prevention and Control

In 2011, World Health Assembly (WHA) Resolution 64.15 urged all member states to “work towards mobilizing sufficient technical and financial resources for coordinated and multisectoral measures for preparation, prevention, and control of cholera, as well as other diarrhoeal diseases” and “to undertake planning for and give consideration to the administration of vaccines, where appropriate” [43]. Within the global context of the large burden of cholera described in Figure 1, any OCV stockpile created to respond to emergencies

(presumably in one or more of the blue dots per year in Figure 1, depending on the size of the stockpile), will certainly help. However, we cannot expect an emergency stockpile alone to lead to significant changes in future versions of Figure 1 since it will not improve cholera control in endemic countries, where OCVs may also play a role [36]. The Global Vaccine Action Plan seeks to extend the full benefits of immunization to all people by 2020 and to make a world “in which all individuals and communities enjoy lives free from vaccine-preventable diseases” [44]. We must recognize cholera as a preventable global threat that preferentially attacks vulnerable populations and crosses international boundaries, and begin to develop national and regional strategic plans that focus on prevention and preparedness. Such plans should ensure the most cost-effective use of limited resources and well-informed responses to individual outbreaks when prevention fails.

The relative cost-effectiveness of OCVs compared to other options for cholera prevention remains uncertain. We hope that creation of the OCV stockpile for emergency response will represent a strong beginning for a global focus on overall management of cholera risks using all of the tools available for both prevention and control. Stakeholders at all levels should see the milestone of creation of an OCV stockpile as a time to assess the risks and risk management opportunities that exist and to begin to collect improved evidence about the benefits, risks, and costs of new OCVs.

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